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PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application of: Ramakrishnan et al.  
Serial No.: 09/905,212  
Filed: July 13, 2001  
Titled: Crystal Structure of Antibiotics Bound  
to the 30S Ribosome and Its Use

Examiner: Ly, Cheyne D.  
Group Art Unit: 1631  
Conf. No.: 3863

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**AMENDMENT AND RESPONSE**

Sir:

This Amendment is being filed in response to the Office Action mailed from the U.S. Patent and Trademark Office on November 17, 2004 in the above-identified application. Reconsideration and further examination are requested.

An extension of time to respond to the Office Action is respectfully requested. A Petition for Extension of Time, a Notice of Appeal, and the appropriate fees are being filed concurrently with this Amendment.

**Amendments to the Claims** are shown in the "Listing of the Claims" which begins on page 2 of this paper.

**Remarks** begin on page 7 of this paper.

Applicants respectfully request entry of the amendments and remarks.

The following Listing of the Claims will replace all prior versions and all prior listings of the claims in the present application:

1. (Previously Presented) A crystal of a prokaryotic 30S ribosomal subunit bound to an antibiotic Z, (wherein Z is defined below), consisting of a tetragonal space group  $P4_12_12$  with unit cell dimensions, for each of the antibiotics Z, of:

Z	a(Angstroms)	b(Angstroms)	c(Angstroms)
Paromomycin	401.375	401.375	175.887
Paromomycin	401.2	401.2	176.4
Streptomycin	401.375	401.475	175.887
Streptomycin	401.375	401.375	175.887
Tetracycline	401.158	401.158	176.994
Pactamycin	401.719	401.719	177.002
Hygromycin B	402.063	402.063	175.263

2. (Previously Presented) A crystal of a prokaryotic 30S ribosomal subunit bound to the antibiotic paromomycin consisting of a tetragonal space group  $P4_12_12$  with unit cell dimensions of  $a = 401.4 \text{ \AA}$ ,  $b = 401.4 \text{ \AA}$ ,  $c = 175.9 \text{ \AA}$ .

3. (Previously Presented) A crystal of a prokaryotic 30S ribosomal subunit bound to the antibiotic paromomycin consisting of a tetragonal space group  $P4_12_12$  with unit cell dimensions of  $a = 402.0 \text{ \AA}$ ,  $b = 402.0 \text{ \AA}$ ,  $c = 176.5 \text{ \AA}$ .

4. (Previously Presented) A crystal of a prokaryotic 30S ribosomal subunit bound to the antibiotic paromomycin consisting of a tetragonal space group  $P4_12_12$  with unit cell dimensions of  $a = 401.2 \text{ \AA}$ ,  $b = 401.2 \text{ \AA}$ ,  $c = 176.4 \text{ \AA}$ .

5. (Previously Presented) A crystal of a prokaryotic 30S ribosomal subunit bound to the antibiotic Streptomycin consisting of tetragonal space group  $P4_12_12$  with unit cell dimensions of  $a = 401.4 \text{ \AA}$ ,  $b = 401.4 \text{ \AA}$ ,  $c = 175.9 \text{ \AA}$ .

6. (Previously Presented) A crystal of a prokaryotic 30S ribosomal subunit bound to the antibiotic Streptomycin consisting of a tetragonal space group  $P4_12_12$  with unit cell dimensions of  $a = 402.0 \text{ \AA}$ ,  $b = 402.0 \text{ \AA}$ ,  $c = 176.5 \text{ \AA}$ .

7. (Previously Presented) A crystal of a prokaryotic 30S ribosomal subunit bound to the antibiotic paromomycin consisting of a tetragonal space group  $P4_12_12$  with unit cell dimensions of  $a = 401.4 \text{ \AA}$ ,  $b = 401.4 \text{ \AA}$ ,  $c = 175.9 \text{ \AA}$ .

8. (Previously Presented) A crystal of a prokaryotic 30S ribosomal subunit bound to the antibiotic Spectinomycin consisting of a tetragonal space group  $P4_12_12$  with unit cell dimensions of  $a = 402.0 \text{ \AA}$ ,  $b = 402.0 \text{ \AA}$ ,  $c = 176.5 \text{ \AA}$ .

9. (Previously Presented) A crystal of a prokaryotic 30S ribosomal subunit bound to the antibiotic Tetracycline consisting of a tetragonal space group  $P4_12_12$  with unit cell dimensions of  $a = 401.2 \text{ \AA}$ ,  $b = 401.2 \text{ \AA}$ ,  $c = 176.9 \text{ \AA}$ .

10. (Previously Presented) A crystal of a prokaryotic 30S ribosomal subunit bound to the antibiotic pactamycin consisting of a tetragonal space group  $P4_12_12$  with unit cell dimensions of  $a = 401.7 \text{ \AA}$ ,  $b = 401.7 \text{ \AA}$ ,  $c = 177.0 \text{ \AA}$ .

11. (Previously Presented) A crystal of a prokaryotic 30S ribosomal subunit bound to the antibiotic Hygromycin B consisting of a tetragonal space group  $P4_12_12$  with unit cell dimensions of  $a = 402.1 \text{ \AA}$ ,  $b = 402.1 \text{ \AA}$ ,  $c = 175.3 \text{ \AA}$ .

12. (Currently Amended) A crystal of a prokaryotic 30S ribosomal subunit bound to the antibiotic selected from the group paromomycin, streptomycin, spectinomycin, tetracycline, pactamycin and hygromycin B, having a resolution of about 3 Å.

13. (Previously Presented) A crystal of a prokaryotic 30S ribosomal subunit bound to an antibiotic consisting of the structure defined by the co-ordinates of a table selected from the group of tables 1 to 4.

14. (Canceled) A computer-based method of rational drug design which comprises:

providing the structure of a 30S ribosomal subunit as defined by the coordinates of a table selected from the group of tables 1 to 4;

providing the structure of a candidate modulator molecule; and

fitting the structure of candidate to the structure of the 30S of said table.

15. (Canceled) A computer-based method for identifying a potential inhibitor of the 30S ribosome comprising the steps of:

a. employing a three-dimensional structure of 30S, or at least one sub-domain thereof, to characterize at least one active site, the three-dimensional structure being defined by atomic coordinate data according to a table selected from the group of tables 1 to 4; and

b. identifying the potential inhibitor by designing or selecting a compound for interaction with the active site.

16. (Canceled) The method of claim 15 which further comprises:

c. obtaining or synthesizing the potential inhibitor;

d. contacting the potential inhibitor with 30S to determine the ability of said inhibitor to interact with 30S.

17. (Canceled) The method of claim 15 which further comprises:

- c. obtaining or synthesizing the potential ligand;
- d. forming a complex of 30S and said potential ligand; and
- e. analyzing said complex by X-ray crystallography to determine the ability of said potential ligand to interact with 30S.

18. (Canceled) A computer-based method of rational drug design which comprises:

providing the coordinates of at least one atom of a table selected from the group of tables 1 to 4 of the 30S ribosome;

providing the structure of a candidate inhibitor molecule;

fitting the structure of candidate to the coordinates of the 30S ribosome provided to obtain a result; and

comparing said result with a structure comprising the coordinates of the 30S ribosome provided and at least one atom from one antibiotic structure of said table.

19. (Canceled) The method of claim 18 wherein the coordinates comprise a subdomain of the 30S ribosome.

20. (Canceled) The method of claim 18 wherein the coordinates are selected from at least none member of any one of the following groups of residues:

Group 1: G1405, A1408, C1490, G1491, A1493, G1494 and U1495;

Group II: G1064, C1066, G1068 and C1192;

Group III: U14, C526, G527, A913, A914, C1490, G1941 and S12Lys45;

Group IV: A965, G966, G1053, C1054, C1195, U1196, G1197 and G1198;

Group V: U244, A892 and C893;

Group VI: G693, A694, C788, C795, C796, S7Gly81, and optionally U1540; and

Group VII: C1403, G1405, G1494, U1495, C1496 and U1498.

21. (Canceled) A computer system, intended to generate structures and/or perform rational drug design for the 30S ribosome or complexes of the 30S ribosome with a potential modulator, the system containing either (a) atomic coordinate data according to a table selected from the group of tables 1 to 4, said data defining the three-dimensional structure of 30S or at least one sub-domain thereof, or (b) structure factor data for 30S, said structure factor data being derivable from the atomic coordinate data of a table selected from the group of tables 1 to 4.

22. (Canceled) A computer readable media, with either (a) atomic coordinate data according to a table selected from the group of tables 1 to 4 recorded thereon, said data defining the three-dimensional structure of 30S ribosome, or at least one atom or at least one sub-domain thereof, or (b) structure factor data for 30S ribosome recorded thereon, the structure factor data being derivable from the atomic coordinate data of a table selected from the group of tables 1 to 4.